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EFFECT OF CERTAIN PSYCHOPHARMACOLOGICAL PREPARATIONS
ON ADAPTATION UNDER STRESS CONDITIONS

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16. Abstract Experiments staged on rats demonstrated that the formation of pathological states caused by stress and accompanied by the development of ulcerative lesion of the gastric mucosa are associated with the degree of the catecholamines level drop in the mesencephalon and hypothalamus. The application of seduxen and also of combinations consisting of L-DOPA with seduxen, or with an L-adrenoblocking agent-pyroxan tends to reduce the frequency of developing ulcerative lesions of the stomach. The protective effect produced by the combination of L-DOPA with an L-adrenoblocking agent--pyroxan is barred by an additional administration of an β -adrenoblocking agent--inderal.					
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EFFECT OF CERTAIN PSYCHOPHARMACOLOGICAL PREPARATIONS
ON ADAPTATION UNDER STRESS CONDITIONS

By

A. V. Stanishevskaya and L. N. Mezentseva*

In the experimental work on animals a study has been made of the change in the /9** content of catecholamines and DOPA in the mesencephalon and hypothalamus, as well as in the adrenals in pathological conditions caused by stress and accompanied by the formation of ulcerous lesions of the stomach mucous membrane. At the same time a study was made of the effectiveness of different neuropharmacological preparations and their combinations, employed to improve adaptation under stress conditions and prevention of the indicated disorders.

Methods of Study

Experiments were conducted on 456 mongrel male rats weighing 220-250 g. The stress state was induced by 3-hour immobilization with simultaneous electrical stimulation (O. N. Zabrodin, 1963).

In the first series of experiments the rats were decapitated directly after the 3-hour stimulation, within 24 and 48 h after it. The stomach, adrenal glands, mesencephalon and hypothalamus were removed. In each experiment an analysis was made of the number of animals with ulcerous lesions and the average number of lesions on one animal. The adrenals were weighed and stained for histochemical determination of noradrenaline and adrenaline in the cerebral layer according to Khilarp and Khokfel'd (A. I. Yakovleva, 1964).

The content of catecholamines, noradrenaline, and dopamine, as well as DOPA in the mesencephalon and hypothalamus were determined fluorometrically (Turler and Kaser, 1971; Laverti and Taylor, 1968). Ten rats were taken in each

*Numbers in margin indicate pagination in original foreign text.

experiment. Statistical processing was done according to Student's method.

In the second series of experiments, 30 minutes before the beginning of immobilization the rats were administered the studied preparations: seduxen 5 mg/kg, inderal 0.5 and 2 mg/kg, phenamine 5 and 10 mg/kg, phentolamine 5 mg/kg, and pyroxan 20 mg/kg, l-DOPA ("Levopa", Yugoslavia) 50 mg/kg (administered on the background of stimulation). Rats exposed to the indicated stress effect without the administration of the preparations served as the control.

Results

Under the influence of 3-hour electrical, painful stimulation the weight of the adrenal glands in the rats killed directly after stress, and killed after 24 hours was significantly increased. Depletion of the catecholamine supplies was observed on the adrenal sections.

Under the influence of stress the noradrenaline content in the mesencephalon ($P < 0.001$) and hypothalamus ($P < 0.01$) was reduced in all the animals. Here, in 88.2% of the rats ulcerous gastric lesions were observed. In these animals the reduction in the concentration of noradrenaline was more pronounced ($P < 0.05$) than in rats without ulcerous stomach. A drop in the level of dopamine in the mesencephalon and hypothalamus ($P < 0.02$) was also more pronounced in the rats with ulcerous lesions than in the animals with unchanged stomachs. The DOPA content in rats exposed to the stress effect both in the mesencephalon and in the hypothalamus did not significantly differ from the control (table 1).

In the second series of experiments in rats who received seduxen before the electrical, painful stimulation, the frequency of gastric lesions was noticeably reduced; the average number of destructive lesions on one animal was also reduced (table 2). Under the influence of l-DOPA the number of ulcerous lesions in rats during stress was not altered (see table 2). The use of 10 mg/kg of phenamine caused the death of all the animals during the stress situation. In a lower dose (5 mg/kg) phenamine induced the death of 30% of the animals. Ulcers formed in all the other animals.

The β -adrenoblocking agent inderal only in a small dose (0.5 mg/kg) reduced the average number of destructive lesions for one animal (see table 2). The α -adrenoblocking agents phentolamine and pyroxan also did not prevent the formation

TABLE 1. CHANGE IN CONTENT OF NORADRENALINE, DOPHAMINE AND DOPA UNDER INFLUENCE OF STRESS IN MESENCEPHALON AND HYPOTHALAMUS IN RATS (M+m)

Section of brain	Substance	Animals with ulcers	P	without ulcers	P ₁	Control
Mesencephalon	Noradrenaline	220.8±13.1	<0.01	272.7±15.7	<0.05	311.7±14.5
	Dopamine	249.9±37.5		369.8±66.4		408.9±53.67
	DOPA	57.8±8.26		66.46±10.2		62.87±7.19
Hypothalamus	Noradrenaline	847.4±29.6	<0.01	939±27.98	<0.05	1133±65
	Dopamine	961.5±37.8		1224±137.1		127.1±89.28
	DOPA	150±13.7		133.9±3.77		143.9±9.92

Note: P is given as compared to the control, P₁ as compared to the animals with ulcerous stomach.

of ulcers in rats under stress conditions (see table 2). With a combination of pyroxan and l-DOPA the ulcerous lesions in the stomach as a result of stress were observed only in 2 of the 9 animals; the sizes of the ulcers were considerably smaller than in the control experiments. The addition of inderal (0.5 mg/kg) to the combination of l-DOPA and pyroxan caused the loss of the protective effect of the two last preparations (see table 2). The combination of l-DOPA with inderal also did not prevent the formation of ulcers as a result of stress (see table 2). The most effective in terms of preventing ulcerous lesions of the stomach under stress was the combination of l-DOPA and seduxen: ulcerous gastric lesions were observed only in 2 of the 15 animals.

Discussion of Results

It is known that the stress situation (immobilization and simultaneous electrical stimulation) results in the development in animals of pathological changes in the internal organs, including, ulcerous lesions of the gastric mucous membrane (S. V. Anichkov et al., 1969; S. V. Anichkov, 1975).

Our studies demonstrated that in rats stress results in the depletion of supplies of noradrenaline in the hypothalamus and the mesencephalon, as well as dopamine in the hypothalamus, while the content of l-DOPA is not altered. Here the most pronounced depletion of catecholamine supplies is observed in those cases where as a result of stress dystrophic lesions were formed in the gastric mucous membrane. Apparently, an important role in the mechanism for the formation of pathological syndromes during stress (for example, ulcerous gastric lesions) is played by the degree of disruption in the activity of the noradrenergic neuro-mediator systems of the hypothalamus and mesencephalon. The use of the tranquilizer

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TABLE 2. EFFECT OF PHARMACOLOGICAL PREPARATIONS ON FORMATION OF ULCEROUS LESIONS OF THE STOMACH IN RATS DURING STRESS

Preparation	Dose, mg/kg.	No. of animals with ulcerous lesions	Total number of animals	Number of lesions per 1 animal ($\bar{M} \pm m$)
Control		90 (88,2%)	102	5,9 \pm 0,25
Seduxen	5	7	21	1,0 \pm 0,14
l-DOPA	50	7	9	5,4 \pm 0,93
Inderal	2	6	6	7,0 \pm 0,44
Pyroxan	20	6	6	4,6 \pm 0,84
Inderal	0,5	5	7	2,5 \pm 0,13
Phentolamine				
l-DOPA	5	6	6	4,4 \pm 0,51
Seduxen	50			
l-DOPA	5	2	15	0,56 \pm 0,48
pyroxan	50			
l-DOPA	20	2	9	0,57 \pm 0,19
pyroxan	50			
pyroxan	20	8	9	4,3 \pm 0,63
inderal	0,5			
l-DOPA	50			
inderal	0,5	6	6	4,2 \pm 0,75

seduxen of the series of benzodiazepines that block the effect of stress on the circulation of noradrenaline in the brain of experimental animals (Corrod et al, 1971), to a considerable degree reduced the formation of ulcerous gastric lesions. On the contrary, phenamine, that releases the catecholamines of the central nervous system and increases the sensitivity of the adrenoreceptors of the brain, intensified the pathological effect of the stressor. The addition of l-DOPA to seduxen increased its protective effect, although the use of l-DOPA itself did not reduce the number of animals with dystrophic lesions of the stomach.

The α adrenoblocking agents phentolamine and pyroxan in our experiments were also ineffective, however the combination of the latter with l-DOPA yielded a distinctly positive effect.

The β -adrenoblocking agent inderal hindered the positive effect of l-DOPA, that appeared on the background of a blockade of the α -adrenoreceptors by pyroxan; although it did not in itself or in combination with l-DOPA induce a defense effect, pyroxan in addition to the combination of l-DOPA completely eliminated its defense effect.

Thus, seduxen, as well as the combination of seduxen and l-DOPA and seduxen and α -adrenoblocking agent pyroxan improve the organism's adaptation to stress conditions and to a considerable degree prevent the development of a pathological syndrome.

Conclusions

1. The central noradrenergic mechanisms participate in the formation of pathological states that occur as a result of stress and are accompanied by ulcerous gastric lesions. The emergence of somatic disorders correlates with the degree of reduction in the level of noradrenaline in the mesencephalon and hypothalamus.

2. Preliminary administration of phenamine (5 and 10 mg/kg) intensifies the pathological effect of the stressor. The administration of the β -adreno-blocking agent inderal (0.5 mg/kg) and α -adrenoblocking agent pyroxan (20 mg/kg) does not have a significant effect on the frequency of ulcerous lesions in the rat stomach under stress.

3. The administration of L-DOPA (50 mg/kg) does not affect the frequency of ulcerous gastric lesions under stress conditions. The defense effect of L-DOPA is manifest during the blocking of the α -adrenoreceptors by pyroxan and is eliminated with the additional blocking of the β -receptors by inderal.

4. The use of the tranquilizer seduxen (5 mg/kg) and its combination with L-DOPA (50 mg/kg) improves the adaptation of the organism under stress conditions and reduces the degree of ulcerous gastric lesions.

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